1. A method for identifying nucleotide sequences encoding interacting polypeptide sequences, the method comprising:

providing a host cell containing a reporter gene operably linked to a transcriptional regulatory sequence which includes a binding site for a DNA-binding domain;

introducing into the host cell a first chimeric gene encoding a first fusion protein, wherein the first fusion protein comprises a first polypeptide sequence and a DNA binding domain, and wherein the first chimeric gene comprises a first nucleotide sequence encoding the first polypeptide sequence;

introducing into the host cell a second chimeric gene encoding a second fusion protein, wherein the second fusion protein comprises a second polypeptide sequence and an activation tag, and wherein the second chimeric gene comprises a second nucleotide sequence encoding the second polypeptide sequence;

culturing the host cell for a time sufficient to allow an interaction of the first fusion protein and the second fusion protein, wherein the interaction results in a measurable change in expression of the reporter gene;

selecting the host cell based upon the measurable change in expression of the reporter gene; and

sequencing the first nucleotide sequence and the second nucleotide sequence, to thereby identify nucleotide sequences encoding interacting polypeptide sequences.

2. The method of claim 1, wherein the host cell is a prokaryotic cell.

3. The method of claim 1, wherein the host cell is a eukaryotic cell.

4. The method of claim 1, wherein the first nucleotide sequence is derived from a nucleic acid library.

5. The method of claim 1, wherein the second nucleotide sequence is derived from a nucleic acid library.

6. The method of claim 1, wherein the first nucleotide sequence and the second nucleotide sequence are derived from nucleic acid libraries.

7. The method of claim 6, wherein the nucleic acid libraries are genomic DNA libraries.

8. The method of claim 7, wherein the genomic DNA libraries are whole genome shotgun genomic libraries.

9. The method of claim 7, wherein the genomic DNA libraries are reduced representation shotgun genomic libraries.

10. The method of claim 7, wherein the genomic DNA libraries are hypomethylated shotgun genomic libraries.

11. The method of claim 7, wherein the genomic DNA libraries are hypermethylated shotgun genomic libraries.

12. The method of claim 6, wherein the nucleic acid libraries are cDNA libraries.

13. The method of claim 6, wherein the nucleic acid libraries are 5' methionine-enriched DNA libraries.

14. The method of claim 1, wherein the sequencing of the first nucleotide sequence and the second nucleotide sequence is carried out without amplifying one or both of the sequences after selecting the host cell based upon the measurable change in expression of the reporter gene.

15. The method of claim 1, wherein the sequencing of the first nucleotide sequence and the second nucleotide sequence is carried out without amplifying either

sequence after selecting the host cell based upon the measurable change in expression of the reporter gene.

16. The method of claim 15, wherein, prior to sequencing, the first nucleotide sequence and the second nucleotide sequence are purified from the host cell in the same compartment of a multi-compartment device.

17. The method of claim 15, wherein, prior to sequencing, the first nucleotide sequence and the second nucleotide sequence are purified from the host cell in the same well of a 96 well vessel.

18. The method of claim 16, wherein sequencing reactions for the first nucleotide sequence and the second nucleotide sequence are carried out in the same well of a 384 well vessel.

19. The method of claim 15, wherein, prior to sequencing, the first nucleotide sequence is purified from the host cell in a first well of a first 96 well vessel and the second nucleotide sequence is purified from the host cell in a second well of a second 96 well vessel, wherein the first and second wells of the first and second 96 well vessels occupy the same relative position in each of the 96 well vessels.

20. The method of claim 19, wherein sequencing reactions for the first nucleotide sequence are carried out in a first well of a first 384 well vessel and sequencing reactions for the second nucleotide sequence are carried out in a second well of a second 384 well vessel, wherein the first and second wells of the first and second 384 well vessels occupy the same relative position in each of the 384 well vessels.

21. The method of claim 1, further comprising preparing a computer readable record comprising an entry which includes a first identifier corresponding to the first polypeptide sequence and a second identifier corresponding to a binding property of the first polypeptide sequence.

22. The method of claim 1, wherein prior to the selecting of the cell based upon the measurable change in expression of the reporter gene, the host cell is placed on a robot compatible substrate which permits automated picking of cells exhibiting the measurable change in expression of the reporter gene.

23. The method of claim 22, further comprising using an automated device to select the host cell exhibiting the measurable change in expression of the reporter gene.

24. A method for identifying nucleotide sequences encoding interacting polypeptide sequences, the method comprising:

providing a cell population comprising a plurality of host cells, wherein each of the plurality of host cells contains a reporter gene operably linked to a transcriptional regulatory sequence which includes a binding site for a DNA-binding domain;

introducing into each of the plurality of host cells a first chimeric gene encoding a first fusion protein, wherein the first fusion protein comprises a first polypeptide sequence and a DNA binding domain, wherein the first chimeric gene comprises a first nucleotide sequence which encodes the first polypeptide sequence, and wherein the first nucleotide sequence is different in the first chimeric gene introduced into each of the plurality of host cells;

introducing into each of the plurality of host cells a second chimeric gene encoding a second fusion protein, wherein the second fusion protein comprises a second polypeptide sequence and an activation tag, wherein the second chimeric gene comprises a second nucleotide sequence which encodes the second polypeptide sequence, and wherein the second nucleotide sequence is different in the second chimeric gene introduced into each of the plurality of host cells;

culturing the plurality of host cells for a time sufficient to allow an interaction of the first fusion protein and the second fusion protein, wherein the interaction results in a measurable change in expression of the reporter gene;

selecting the plurality of host cells based upon the measurable change in expression of the reporter gene; and

sequencing the first nucleotide sequence and the second nucleotide sequence contained in each of the plurality of host cells, to thereby identify nucleotide sequences encoding interacting polypeptide sequences.

25. The method of claim 24, wherein the plurality of host cells comprises at least 100 cells.

26. The method of claim 25, wherein the plurality of host cells comprises at least 1,000 cells.

27. The method of claim 26, wherein the plurality of host cells comprises at least 10,000 cells.

28. The method of claim 27, wherein the plurality of host cells comprises at least 100,000 cells.

29. The method of claim 28, wherein the plurality of host cells comprises at least 1,0000,000 cells.

30. The method of claim 29, wherein the plurality of host cells comprises at least 10,000,000 cells.

31. The method of claim 30, wherein the plurality of host cells comprises at least 100,000,000 cells.

32. The method of claim 31, wherein the plurality of host cells comprises at least 1,000,000,000 cells.

33. The method of claim 24, wherein at least 1,000 different first chimeric genes are introduced into the plurality of host cells.

34. The method of claim 33, wherein at least 10,000 different first chimeric genes are introduced into the plurality of host cells.

35. The method of claim 34, wherein at least 100,000 different first chimeric genes are introduced into the plurality of host cells.

36. The method of claim 24, wherein at least 1,000 different second chimeric genes are introduced into the plurality of host cells.

37. The method of claim 36, wherein at least 10,000 different second chimeric genes are introduced into the plurality of host cells.

38. The method of claim 37, wherein at least 100,000 different second chimeric genes are introduced into the plurality of host cells.

39. The method of claim 26, wherein the plurality of host cells are prokaryotic cells.

40. The method of claim 26, wherein the plurality of host cells are eukaryotic cells.

41. The method of claim 26, wherein a first DNA-binding domain is encoded by the first chimeric gene introduced into a first subset of the plurality of host cells, and wherein a second DNA-binding domain is encoded by the first chimeric gene introduced into a second subset of the plurality of host cells.

42. The method of claim 41, wherein a third DNA-binding domain is encoded by the first chimeric gene introduced into a third subset of the plurality of host cells.

43. The method of claim 26, wherein the DNA-binding domain is fused to the amino terminus of the first polypeptide sequence in a first subset of the plurality of host

cells, and wherein the DNA-binding domain is fused to the carboxy terminus of the first polypeptide sequence in a second subset of the plurality of host cells.

44. The method of claim 26, wherein a first activation tag is encoded by the second chimeric gene introduced into a first subset of the plurality of host cells, and wherein a second activation tag is encoded by the second chimeric gene introduced into a second subset of the plurality of host cells.

45. The method of claim 44, wherein a third activation tag is encoded by the second chimeric gene introduced into a third subset of the plurality of host cells.

46. The method of claim 39, wherein the first nucleotide sequence is derived from a nucleic acid library.

47. The method of claim 39, wherein the second nucleotide sequence is derived from a nucleic acid library.

48. The method of claim 39, wherein the first nucleotide sequence and the second nucleotide sequence are derived from nucleic acid libraries.

49. The method of claim 48, wherein the nucleic acid libraries are genomic DNA libraries.

50. The method of claim 49, wherein the genomic DNA libraries are whole genome shotgun genomic libraries.

51. The method of claim 49, wherein the genomic DNA libraries are reduced representation shotgun genomic libraries.

52. The method of claim 49, wherein the genomic DNA libraries are hypomethylated shotgun genomic libraries.

53. The method of claim 49, wherein the genomic DNA libraries are hypermethylated shotgun genomic libraries.

54. The method of claim 48, wherein the nucleic acid libraries are cDNA libraries.

55. The method of claim 48, wherein the nucleic acid libraries are 5' methionine-enriched DNA libraries.

56. The method of claim 26, wherein the sequencing of the first nucleotide sequence and the second nucleotide sequence in each of the host cells is carried out without amplifying either sequence after selecting the plurality of host cells based upon the measurable change in expression of the reporter gene.

57. The method of claim 56, wherein, prior to sequencing, the first nucleotide sequence and the second nucleotide sequence for each of the plurality of host cells are purified from the respective host cells in the same well of a 96 well vessel.

58. The method of claim 57, wherein sequencing reactions for the first nucleotide sequence and the second nucleotide sequence for each of the plurality of host cells are carried out in the same well of a 384 well vessel.

59. The method of claim 26, wherein prior to selecting of the cells based upon the measurable change in expression of the reporter gene, the plurality of host cells are placed on a robot compatible substrate which permits automated picking of cells exhibiting the measurable change in expression of the reporter gene.

60. The method of claim 59, further comprising using an automated device to pick the plurality of host cells exhibiting the measurable change in expression of the reporter gene.

61. The method of claim 60, wherein the plurality of host cells are prokaryotic cells.

62. The method of claim 61, wherein after selecting of the cells based upon the measurable change in expression of the reporter gene, the first nucleotide sequence and the second nucleotide sequence are purified from the plurality of host cells and sequenced without amplification of the sequences prior to the carrying out of the sequencing step.

63. The method of claim 62, wherein the first nucleotide sequence and the second nucleotide sequence of each of the plurality of host cells are purified in the same vessel.

64. The method of claim 63, wherein the first nucleotide sequence and the second nucleotide sequence of the plurality of host cells are purified in wells of 96 well vessels.

65. The method of claim 64, wherein sequencing reactions for each of the first nucleotide sequence and the second nucleotide sequence of the plurality of host cells are carried out in wells of 384 well vessels.

66. The method of claim 64, wherein the sequencing comprises single-plex sequencing of the first nucleotide sequence and the second nucleotide sequence.

67. The method of claim 64, wherein the sequencing reactions in the wells of the 384 well vessels is carried out using a reaction volume of 25 µl or less.

68. The method of claim 64, wherein reaction products of the sequencing reactions are transferred directly from the well of the 384 well vessel to a capillary, microfabricated, or single molecule DNA sequencer.

69. The method of claim 24, further comprising preparing a computer readable record comprising a plurality of entries, each entry comprising a first identifier which

corresponds to a first polypeptide sequence and a second identifier which corresponds to a binding property of the first polypeptide sequence.

70. A method for identifying nucleotide sequences encoding interacting polypeptide sequences, the method comprising:

providing a cell population comprising 100,000 bacterial host cells, wherein each of the 100,000 bacterial host cells contains a reporter gene operably linked to a transcriptional regulatory sequence which includes a binding site for a DNA-binding domain;

introducing into each of the 100,000 bacterial host cells a first chimeric gene encoding a first fusion protein, wherein the first fusion protein comprises a first polypeptide sequence and a DNA-binding domain, wherein the first chimeric gene comprises a first nucleotide sequence which encodes the first polypeptide sequence, and wherein the first nucleotide sequence is different in the first chimeric gene introduced into each of the 100,000 bacterial host cells;

introducing into each of the 100,000 bacterial host cells a second chimeric gene encoding a second fusion protein, wherein the second fusion protein comprises a second polypeptide sequence and an activation tag, wherein the second chimeric gene comprises a second nucleotide sequence which encodes the second polypeptide sequence, and wherein the second nucleotide sequence is different in the second chimeric gene introduced into each of the 100,000 bacterial host cells;

culturing the 100,000 bacterial host cells for a time sufficient to allow an interaction of the first fusion protein and the second fusion protein, if present, wherein the interaction results in a measurable change in expression of the reporter gene;

selecting from the 100,000 bacterial host cells those cells that exhibit the measurable change in expression of the reporter gene, to thereby result in selected bacterial host cells; and

sequencing the first nucleotide sequence and the second nucleotide sequence contained in selected bacterial host cells, to thereby identify nucleotide sequences encoding interacting polypeptide sequences.

71. A method for identifying nucleotide sequences encoding interacting polypeptide sequences, the method comprising:

providing a cell population comprising a plurality of host cells, wherein each of the plurality of host cells contains a reporter gene operably linked to a transcriptional regulatory sequence which includes a binding site for a DNA-binding domain;

introducing into each of the plurality of host cells a first chimeric gene encoding a first fusion protein, wherein the first fusion protein comprises a first polypeptide sequence and a DNA binding domain, and wherein the first chimeric gene comprises a first nucleotide sequence encoding the first polypeptide sequence;

introducing into each of the plurality of host cells a second chimeric gene encoding a second fusion protein, wherein the second fusion protein comprises a second polypeptide sequence and an activation tag, wherein the second chimeric gene comprises a second nucleotide sequence which encodes the second polypeptide sequence, and wherein the second nucleotide sequence is different in the second chimeric gene introduced into each of the plurality of host cells;

culturing the plurality of host cells for a time sufficient to allow an interaction of the first fusion protein and the second fusion protein, if present, wherein the interaction results in a measurable change in expression of the reporter gene;

selecting from the plurality of host cells those cells that exhibit the measurable change in expression of the reporter gene, to thereby result in selected host cells;

purifying the second nucleotide sequence from each of the selected host cells, wherein the purification is carried out by an automated process in compartments of a multi-compartment device; and

sequencing the second nucleotide sequence from each of the selected host cells, to thereby identify nucleotide sequences encoding interacting polypeptide sequences.

72. The method of claim 71, wherein the second nucleotide sequences from each of the selected host cells are purified in wells of a 96 well vessel.

73. The method of claim 72, wherein sequencing reactions for the second nucleotide sequences are carried out in wells of a 384 well vessel.

74. A method for identifying nucleotide sequences encoding interacting polypeptide sequences, the method comprising:

providing a cell population comprising a plurality of host cells, wherein each of the plurality of host cells contains a reporter gene operably linked to a transcriptional regulatory sequence which includes a binding site for a DNA-binding domain;

introducing into each of the plurality of host cells a first chimeric gene encoding a first fusion protein, wherein the first fusion protein comprises a first polypeptide sequence and a DNA binding domain, wherein the first chimeric gene comprises a first nucleotide sequence which encodes the first polypeptide sequence, and wherein the first nucleotide sequence is different in the first chimeric gene introduced into each of the plurality of host cells;

introducing into each of the plurality of host cells a second chimeric gene encoding a second fusion protein, wherein the second fusion protein comprises a second polypeptide sequence and an activation tag, and wherein the second chimeric gene comprises a second nucleotide sequence encoding the second polypeptide sequence;

culturing the plurality of host cells for a time sufficient to allow an interaction of the first fusion protein and the second fusion protein, if present, wherein the interaction results in a measurable change in expression of the reporter gene;

selecting from the plurality of host cells those cells that exhibit the measurable change in expression of the reporter gene, to thereby result in selected host cells;

purifying the first nucleotide sequence from each of the selected host cells, wherein the purification is carried out by an automated process in compartments of a multi-compartment device; and

sequencing the first nucleotide sequence from each of the selected host cells, to thereby identify nucleotide sequences encoding interacting polypeptide sequences.

75. The method of claim 74, wherein the first nucleotide sequences from each of the selected host cells are purified in wells of a 96 well vessel.

76. The method of claim 75, wherein sequencing reactions for the first nucleotide sequences are carried out in wells of a 384 well vessel.

77. The method of claim 1, further comprising shotgun sequencing a nucleic acid library or the genome of an organism or a virus, wherein the method identifies in serial or in parallel via a two-hybrid assay the protein-protein interactions of polypeptides encoded by the nucleic acid library or the genome of the organism or virus.

78. The method of claim 77, wherein nucleic acid vectors used to carry out the shotgun sequencing are the same as the nucleic acid vectors used to carry out the two-hybrid assay.

79. The method of claim 77, wherein the method identifies in serial the protein-protein interactions of polypeptides encoded by the nucleic acid library or the genome of the organism or virus.

80. The method of claim 77, wherein the method identifies in parallel the protein-protein interactions of polypeptides encoded by the nucleic acid library or the genome of the organism or virus.

81. The method of claim 1, wherein the selected host cell is grown, prior to sequencing of the first and second nucleotide sequences, in a well of a plate having at least 96 wells.

82. The method of claim 71, wherein each of the selected host cells are grown, prior to sequencing of the second nucleotide sequence from each of the selected host cells, in wells of plates having at least 96 wells.

83. The method of claim 74, wherein each of the selected host cells are grown, prior to sequencing of the first nucleotide sequence from each of the selected host cells, in wells of plates having at least 96 wells.